petitions - $
111-1090.00 DA/C for Pat.

BOX PATENT EXT.

#12

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Atty. Docket No. 30472/306

In re: U.S. Patent No. 4,362,567

Patentee: Otto SCHWARZ *et al.*

Assignee: Immuno Aktiengesellschaft für chemish-medizinische Produkte

Issue Date: December 7, 1982

REQUEST FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX PATENT EXT.

Sir:

Pursuant to Section 201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. § 156, Immuno Aktiengesellschaft für chemsih-medizinishe Produkte ("Immuno AG"), the owner of record of the above-identified patent, hereby requests an extension of the patent term of U.S. Patent No. 4,362,567. Immuno AG is now owned by Baxter Healthcare Corp.

The following information is submitted in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. § 1.740.

07/14/1998	**00000001**	**2**	**111**	**$30.00**	**06/26/1998**	**DA 190741**
07/14/1998	**00000002**	**2**	**111**	**$1,090.00**	**06/26/1998**	**CK**

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is a two-component fibrin sealant, vapor heated kit. The product is marketed under the trade-name TISSEEL VH KIT and is available in 0.5mL, 1.0mL, 2.0mL, and 5.0mL kits.

The TISSEEL VH KITS contain four components: (1) Sealer Protein Concentrate (Human), (2) Fibrinolysis Inhibitor (Bovine), (3) Thrombin (Human), and (4) Calcium Chloride Solution. The characteristics of each of these components is set forth in the table below.

		Kit Size			
		0.5mL	*1.0mL*	*2.0mL*	*5.0mL*
Sealer Protein Concentrate White to off-white, freeze-dried substance	Fibrinogen (mg):	37.5-57.5	75-115	150-230	375-575
	Total Protein (mg):	50-65	100-130	200-260	500-650
	Polysorbate 80 (mg)	0.1-0.2	0.2-0.4	0.4-0.8	1-2
	Sodium Chloride (mg)	1-2	2-4	4-8	10-20
	Trisodium Citrate (mg)	2-4	4-8	8-16	20-40
	Glycine (mg)	7.5-17.5	15-35	30-70	75-175
Fibrinolysis Inhibitor Solution Colorless solution	Aprotinin (KIU)	1500	3000	6000	15000
	Volume (mL)	0.5	1	2	5
Thrombin White to off-white, freeze-dried substance	Thrombin (IU)	250	500	1000	2500
	Total Protein (mg)	22.5-27.5	45-55	90-110	225-275
	Sodium Chloride (mg)	4-6	8-12	16-24	40-60
	Glycine (mg)	1.2-1.8	2.4-3.6	4.8-7.2	12-18
Calcium Chloride Solution Colorless solution	$CaCl_2$ (μmol)	20	40	80	200
	Volume (mL)	0.5	1	2	5
Total Combined Volume (mL)		1	2	4	10

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review of the fibrin sealant product occurred under § 351(a) of the Public Health Service Act ("PHSA"), 42 U.S.C. § 262(a), as amended by the Food and Drug Administration Modernization Act of 1997 ("FDAMA"), Public Law 105-1. Section 351(a) provides for the approval of Biologics Licenses.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

The product was approved by the FDA for commercial marketing and use, pursuant to § 351(a) of the PHSA, as amended, on May 1, 1998. See Exhibit A.

(4) In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved:

The approved product comprises the following active ingredients: (1) Sealer Protein Concentrate (Human), (2) Fibrinolysis Inhibitor (Bovine), (3) Thrombin (Human), and (4) Calcium Chloride Solution. The approved product is the first approved fibrin sealant and is approved for use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of plenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical, and as an adjunct for the closure of colotomies (hereinafter "the approved indications").

The Sealer Protein Concentrate contains fibrinogen as the main active ingredient. To the best of applicant's knowledge, fibrinogen has not been previously approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act for any use. The Sealer Protein Concentrate also contains aprotinin. An aprotinin product is approved for use in prophylactic use to reduce perioperative blood loss/need for transfusion in select coronary patients. Aprotinin has not been previously approved for use in a fibrin sealant. The Sealer Protein Concentrate also contains heparin. Heparin is approved for use as an anticoagulent. To the best of applicant's knowledge, heparin has not been previously approved for use in a fibrin sealant. The Sealer Protein Concentrate also contains albumin and cold-insoluble globulin. To the best of applicant's knowledge, neither of these proteins has been previously approved. Because the approved product is the first fibrin sealant product approved by the FDA, none of these ingredients has been previously approved for the approved indications.

The Fibrinolysis Inhibitor contains aprotinin. As mentioned above, an aprotinin product is approved for use in prophylactic use to reduce perioperative blood loss/need for transfusion in select coronary patients. Aprotinin has not been previously approved for use in a fibrin sealant.

To the best of applicant's knowledge, thrombin has not previously been approved for commercial marketing or use under the Federal Food, Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act for any use. Because the approved product is the first fibrin sealant product approved by the FDA, thrombin has not been previously approved for the approved indications.

The Calcium Chloride Solution contains a non-pyrogenic solution of calcium chloride. To the best of applicant's knowledge, such a solution has never been approved for use in a fibrin sealant for the approved indications.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the last day on which the application could be submitted:

The approved product was approved for commercial marketing and use on May 1, 1998. The last day within the sixty day period set forth in 37 C.F.R. § 1.720(f) therefore is June 29, 1998. The date of submission of the present application is on or before this date. The present application therefore has been timely filed within the sixty day period.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. Patent No. 4,362,567

Inventors:	Otto Schwarz; Yendra Linnau; Franz Löblich; Thomas Seelich
Issue Date:	December 7, 1982
Expiration Date:	February 4, 2000, based on a filing date of February 4, 1980

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent 4,362,567 is attached as Exhibit B.

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or re-examination certificate issued in the patent:

U.S. Patent 4,362,567 issued from an application filed before December 12, 1980, and thus no maintenance fees were due. Accordingly, no maintenance fees were paid.

No disclaimer, certificate of correction or re-examination certificate has issued in connection with U.S. Patent No. 4,362,567.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or method of using or manufacturing the approved product:

The claims of US Patent No. 4,362,567 recite a necessary intermediate to the approved product.

Claim 1 of US Patent No. 4,362,567 recites a lyophilized tissue adhesive of mammalian protein origin which comprises fibrinogen, albumin, factor XIII, cold-insoluble globulin and plasminogen-activator inhibitor or plasmin-inhibitor. According to claim 1, fibrinogen is present in at least 33% by weight, the ratio of factor XIII to fibrinogen, expressed in units of factor XIII per gram of fibrinogen , is at least 80, and fibrinogen and albumin are present in a ratio of 33 to 90:5 to 40.

The approved product is a fibrin sealant. One of the active ingredients of this approved product is the Sealer Protein Concentrate. The Sealer Protein Concentrate is a lyophilized substance that contains the main active ingredient fibrinogen, and other ingredients. The Sealer Protein Concentrate is made from frozen plasma (human) from which a precipitate is separated. The precipitate is treated with a buffer to remove inert proteins, centrifuged to obtain the sealer proteins, and then frozen. The frozen proteins are then further formulated by dissolution in a second buffer and then are freeze-dried. Prior to labeling and packaging, the above product is subjected to vapor heat treatment to inactivate viruses. A byproduct of the vapor heating step is the loss of Factor XIII activity. The product then is reconstituted, subjected to sterilizing filtration, sterile filtering, freeze-drying, and quality control measures. The resulting product is the Sealer Protein Concentrate marketed in the approved product.

Prior to the vapor heat treatment, the product described above is covered by the claims of US patent 4,362,567. The product prior to vapor heat treatment contains greater than 33% by

weight fibrinogen, Factor XIII, expressed in units of factor XIII per gram of fibrinogen, in an amount of least 80, the plasminogen-activator inhibitor or plasmin-inhibitor aprotinin in an amount between 250-25,000 KIU per gram of fibrinogen, heparin in an amount between 0.2-200 IU heparin per gram of fibrinogen, and albumin and cold-insoluble globulin such that the ratio of fibrinogen to albumin to cold-insoluble globulin in the total protein is 33 to 90:5 to 40:0.2 to 15. Thus, it is covered by claim 1.

Claim 2 recites the tissue adhesive of claim 1 wherein the plasminogen-activator inhibitor or plasmin-inhibitor is aprotinin. Thus, the product described above also is embodied in claim 2.

Claim 3 recites the tissue adhesive of claim 1 wherein the plasminogen-activator inhibitor or plasmin-inhibitor is present in an amount which is equivalent to 250 to 25,000 KIU per gram of fibrinogen. Thus, the product described above also is embodied in claim 3.

Claim 5 recites the tissue adhesive of claim 1 wherein the adhesive also contains 0.2 to 200 IU heparin per gram of fibrinogen. Thus, the product described above also is embodied in claim 5.

Claim 6 recites the tissue adhesive of claim 1 wherein the ratio of fibrinogen to albumin to cold-insoluble globulin in the total protein is 33 to 90:5 to 40:0.2 to 15.. Thus, the product described above also is embodied in claim 6.

(10) A statement, beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. § 156(g) in order to enable the Secretary of Health and Human Services to determine the applicable regulatory review period as follows:

> **(i) For a patent claiming a human drug, antibiotic or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved or the Product License issued:**

On May 10, 1984, Österreichisches Institut für Haemoderivate Ges.m.b.H. ("ÖIH"), the manufacturer of the approved product for the owner of U.S. Patent No. 4,362,567, submitted to the FDA an IND for the approved product. See Exhibit C. The FDA received the IND on May 21, 1984. The IND was assigned Code No.: BB-IND 2027 and became effective on June 20, 1984, thirty days after May 21, 1984, the date of receipt of the IND by the FDA. Receipt of the "Notice of Claimed Investigational Exemption for a New Drug" was acknowledged by the FDA in a letter dated August 2, 1984. See Exhibit D. This establishes the beginning of the "regulatory review period" for the approved product under 35 U.S.C. § 156(g)(1) as June 20, 1984.

On October 5, 1987, ÖIH submitted an PLA for the approved product, along with the necessary data for a supplement to an Establishment License Application ("ELA"). See Exhibit E. A copy of a letter, dated November 4, 1987, by the FDA acknowledging receipt of the PLA submission is attached hereto as Exhibit F. The PLA was assigned reference No. 87-0509. The ELA supplement was assigned reference No. 87-0508.

The PLA for the approved product was approved on May 1, 1998. Attached hereto as Exhibit A is a copy of the approval letter dated May 1, 1998, from the FDA to ÖIH. Thus, for the purpose of determining the "regulatory review period" under 35 U.S.C. § 156(g)(1), May 1, 1998, is the date of the first approval of the product.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), ÖIH submitted an IND for the approved product on May 10, 1984, and submitted a PLA and related supplemental ELA for the approved product on October 5, 1987. Subsequent to the submission of the IND and PLA, ÖIH had numerous contacts and meetings with the FDA with respect to the applications. These contacts and meetings are summarized in attached Exhibit G entitled "FILE HISTORY: TWO COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT."

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension

35 U.S.C. § 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if the following requirements (1)-(5) are satisfied:

(1) the term of the patent has not expired before an application for extension is submitted.

The term of U.S. Patent No. 4,362,567, expires on February 4, 2000. This application has been submitted before the expiration of the patent term. Accordingly, this requirement is satisfied.

(2) the term of the patent has never been extended.

The term of U.S. Patent No. 4,362,567 never has been extended. Accordingly, this requirement is satisfied.

(3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. § 156(d).

This application is submitted by an agent of the owner of record, Immuno AG. This application is submitted in accordance with 35 U.S.C. § 156(d) in that it is submitted within the sixty-day period beginning on the date that the approved product received permission for commercial marketing and use under the PHSA and contains the information required under 35 U.S.C. § 156(d). Accordingly, this requirement is satisfied.

(4) the product has been subject to a regulatory review period before its commercial marketing or use.

As evidenced by the May 1, 1998, letter from the FDA, see Exhibit A, the approved product was subject to a regulatory review period under § 351(a) of the PHSA before its commercial marketing or use. Accordingly, this requirement is satisfied.

> (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.

The permission for the commercial marketing and use of the fibrin sealant product granted May 1, 1998, after regulatory review under § 351(a) of the PHSA, is the first permitted commercial marketing or use of the product in the United States. Accordingly, this requirement is satisfied.

Because each of these requirements is satisfied, this patent is eligible for an extension.

Statement as to Length of Extension Claimed

The term of U.S. Patent No. 4,362,567 should be extended by 1,827 days, or until February 4, 2005. This term of extension was determined on the following basis:

As set forth in 35 U.S.C. § 156(g)(1)(B), the regulatory review period equals the sum of the following periods (i) and (ii):

> (i) the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 became effective for the approved product and ending on the date an application was initially submitted for such drug product under section 351, 505, or 507.

An IND for the product was effective on June 20, 1984. The PLA for the product was submitted on October 5, 1987. Thus, for the purpose of this calculation, item (i) for the product equals the number of days from June 20, 1984, to October 5, 1987, or 1,203 days.

> (ii) the period beginning on the date the application was initially submitted for the approved product under section 351, subsection (b) of section 505, or section 507 and ending on the date such application was approved under such section..

The PLA for the product was submitted on October 5, 1987. The PLA was approved on May 1, 1998. Thus, for the purpose of this calculation, item (ii) equals the number of days from October 5, 1987, to May 1, 1998, or 3,862 days.

In accordance with 35 U.S.C. § 156(c), the term of a patent eligible for extension shall be extended by the time equal to the regulatory review period for the approved product which occurred after the date the patent issued. U.S. Patent No. 4,362,567 issued on December 7, 1982. The entire regulatory review period calculated above occurred after this issue date.

35 U.S.C. § 156(c) also sets forth the following exceptions (1)-(3) which may operate to shorten the length of the review period used to calculate patent term extension:

> (1) each period is reduced by any period during which the applicant did not act with due diligence.

In this case, there has been no lack of due diligence during the period of regulatory review calculated above. Accordingly, no reduction in the review period is required by this provision.

(2) each period includes only one-half of the number of days in phase (i).

One-half of the number of days in phase (i) equals one-half of 1,203, or 601.5 days, or 602 days. Adding this number of days to the number of days in phase (ii) (3,862 days) results in a review period of 4,464 days.

> (3) if the period remaining in the patent term after the date of approval of the approved product when added to the regulatory review period as revised under paragraphs (1) and (2) above exceeds fourteen years, the period of extension shall be reduced so that the sum of both periods does not exceed fourteen years.

On the date of approval of the product, May 1, 1998, 1 year and 279 days remained in the term of U.S. Patent No. 4,362,567. Adding this period to the review period calculated above yields a period of less than fourteen years. This provision, therefore, does not operate to shorten the period of extension to which U.S. Patent No. 4,362,567 is entitled.

35 U.S.C. § 156(g)(6) limits the period of patent term extension to a maximum of five years from the original expiration date of the patent. The original expiration date of U.S. Patent 4,362,567 is February 4, 2000. Accordingly, the maximum extension allowed by this provision would extend the term to February 4, 2005. Extension of the patent by the number of days calculated above would extend the patent beyond February 4, 2005. Accordingly, pursuant to 35 U.S.C. § 156(g)(6), US Patent 4,362,567 cannot be extended beyond February 4, 2005.

Thus, U.S. Patent 4,362,567 is entitled to an extension until February 4, 2005, or 1,827 days.

(13) A statement that applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought:

Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to any determination of entitlement to the extension sought.

(14) The prescribed fee for receiving and acting upon the application for extension:

Pursuant to 37 C.F.R. § 1.20(j)(1), a check in the amount of $1,090 is enclosed with this application.

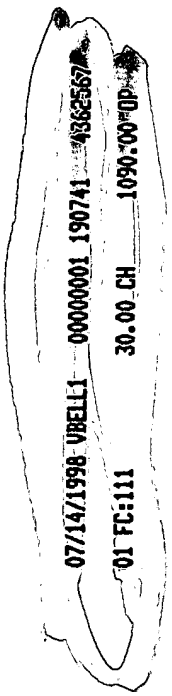
Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees. Should a refund of fee paid be necessary, the Commissioner is hereby authorized to credit any such amount to Deposit Account No. 19-0741.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

John P. Isacson
FOLEY & LARDNER
Washington Harbour, Suite 500
3000 K Street, N. W.
Washington, D. C. 20007-5109
TEL: (202) 672-5477
FAX: (202) 672-5399

(16) A duplicate of the application papers, certified as such:

A duplicate of the application papers, certified as such, is submitted herewith.



(17) An oath or Declaration as set forth in 37 C.F.R. § 1.740(b):

DECLARATION

As agent for the owner of record of U.S. Patent 4,362,567 who has applied for an extension of the term of this patent, I declare that:

(1) I am a patent attorney authorized to practice before the Patent and Trademark Office and who has general authority from the owner of US Patent 4,362,567 to act on behalf of the owner in patent matters;

(2) I have reviewed and understand the contents of this application, which is submitted pursuant to 37 C.F.R. § 1.740 for extension of U.S. Patent 4,362,567;

(3) I believe that U.S. Patent 4,362,567 is subject to extension pursuant to 37 C.F.R. § 1.710;

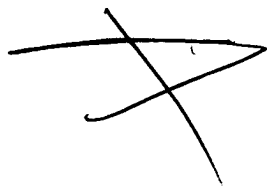
(4) I believe an extension of the length claimed is justified under 35 U.S.C. § 156 and the applicable regulations; and

(5) I believe that U.S. Patent 4,362,567, for which this extension is sought, meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. § 1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application and any extension of U.S. Patent No. 4,362,567.

June 26, 1998
Date

John P. Isacson
Reg. No. 33,715



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

May 1, 1998

Our Reference Numbers: 87-0508 and 87-0509

Herwig Igel, Ph.D.
Österreichisches Institut für Haemoderivate Ges.m.b.H.
Industriestrasse 67
A- 1220 Vienna
Austria

Dear Dr. Igel:

Enclosed please find Biologics License 2.55 issued in accordance with the provisions of Section 35 1 (a) of the Public Health Service Act, as amended by the Food and Drug Administration Modernization Act of 1997 (Public Law 105-l 15). This license authorizes Institut für Haemoderivate Ges.m.b.H. to manufacture and ship for sale, barter or exchange in interstate and foreign commerce Fibrin Sealant for which your company has demonstrated compliance with establishment and product standards. Fibrin Sealant is indicated for use as an adjunct to hemostasis in surgeries involving cardiopulmonary bypass and treatment of splenic injuries due to blunt or penetrating trauma to the abdomen, when control of bleeding by conventional surgical techniques, including suture, ligature, and cautery, is ineffective or impractical. Fibrin Sealant is also indicated as an adjunct for the closure of colostomies.

Under this license you are authorized to manufacture and ship for sale, barter, or exchange Fibrin Sealant in 0.5 mL, 1 .O mL, 2.0 mL, and 5.0 mL kits. The Sealer Protein Concentrate (Human) and Thrombin (Human) components will be manufactured, vapor-heated, formulated, and freeze-dried at your facility in Vienna, Austria. The Fibrinolysis Inhibitor Solution (Bovine) and Calcium Chloride Solution will be formulated and filled at your facility in Vienna, Austria from components as specified in your license application. Fibrinolysis Inhibitor will be produced from bovine material sourced from counties certified free of bovine spongiform encephalopathy. Nonbiological kit components will be supplied by contract manufacturers as specified in your license application. Fibrin Sealant will be distributed by Baxter Healthcare Corporation and Haemacure Corporation. Changes to the product, production process, location of production process, equipment, facilities, or responsible personnel are required to be reported to FDA as specified in Title 21 Code of Federal Regulations (CFR) Section 601.12.

The dating period for the individual components of this product shall be as follows: i) for the Sealer Protein Concentrate (Human) and Thrombin (Human), 24 months from the date of manufacture when stored at 2-8°C; ii) for the Fibrinolysis Inhibitor Solution (Bovine), 36 months from the date of manufacture when stored at 2-8°C; and iii) for the Calcium Chloride Solution, 5 years from the date of manufacture when stored at or below 25°C. The date of manufacture shall be defined as the date of sterile filtration for the Sealer Protein Concentrate (Human), Thrombin (Human), and Fibrinolysis Inhibitor Solution (Bovine). The date of manufacture shall be defined as the date of terminal sterilization for the Calcium Chloride Solution. The dating period for the Fibrin Sealant kits shall not exceed that of any of the components included therein when stored at 2-8°C. Results of ongoing stability studies should be submitted throughout the dating period as they become available.

You are requested to submit samples of each future lot of this product together with protocols showing results of all applicable tests. No lots of product shall be distributed until notification of release is received from the Director, Center for Biologics Evaluation and Research (CBER).

All adverse experience reports should be submitted according to 21 CFR 600.80 to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, Maryland 20852-1448. It is also requested that distribution reports be submitted according to 2 1 CFR 600.8 1.

Please submit three (3) copies of final printed labeling at the time of use accompanied by Part II of FDA 2567 with completed implementation information. In addition, you may wish to submit your proposed introductory advertising and promotional campaign. If so, please submit three (3) copies of the proposed material in draft form with Part I of the FDA Form 2567 to CBER, Advertising and Promotional Labeling Staff (APLS), HFM-202, 1401 Rockville Pike, Rockville, Maryland 20852-1448. Promotional claims should be consistent with and not contrary to the approved labeling. No comparative claims or claims of superiority over other similar products should be made unless data to support such claims are submitted to and approved by CBER. Final copies of advertising and promotional materials should be submitted at the time of use with Part II of FDA Form 2567 to APLS. Please include copies of the approved labeling with your proposed or final copy of advertising and promotional materials submitted to CBER.

Please acknowledge receipt of the enclosed Biologics License to the Director, Division of Blood Applications, HFM -370, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

Sincerely yours,

Jay S. Epstein, M.D.
Director
Office of Blood Research and Review
Center for Biologics Evaluation
and Research

Jerome A. Donlon, M.D., Ph.D.
Director
Office of Establishment Licensing
and Product Surveillance
Center for Biologics Evaluation
and Research

United States Patent [19]

Schwarz et al.

[11] **4,362,567**

[45] **Dec. 7, 1982**

[54] **TISSUE ADHESIVE**

[75] Inventors: **Otto Schwarz; Yendra Linnau; Franz Löblich; Thomas Seelich**, all of Vienna, Austria

[73] Assignee: **Immuno Aktiengesellschaft für chemisch-medizinische Produkte**, Vienna, Austria

[21] Appl. No.: **118,529**

[22] Filed: **Feb. 4, 1980**

[30] **Foreign Application Priority Data**

Feb. 15, 1979 [AT] Austria 1189/79

[51] Int. Cl.³ **A61K 3/14**; C09J 3/24

[52] U.S. Cl. **106/157**; 106/124; 106/126; 424/101; 424/177

[58] Field of Search 106/124, 157, 126; 424/101, 177

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,523,807 8/1970 Gerendas 106/124

FOREIGN PATENT DOCUMENTS

448302 5/1948 Canada 106/124

Primary Examiner—Allan Lieberman

Attorney, Agent, or Firm—Brumbaugh, Graves, Donohue & Raymond

[57] **ABSTRACT**

A tissue adhesive on the basis of human or animal protein contains factor XIII and at least 33% by weight of fibrinogen, has a ratio of factor XIII to fibrinogen, expressed in units of factor XIII per gram of fibrinogen, of at least 80, contains fibrinogen and albumin in the total protein at a ratio of 33 to 90:5 to 40, contains plasminogen-activator-inhibitor or plasmin inhibitor in an amount of 250 to 25,000 KIU per g of fibrinogen and has been lyophilized.

9 Claims, No Drawings

TISSUE ADHESIVE

The invention relates to a tissue adhesive on the basis of human or animal proteins, containing fibrinogen and factor XIII.

It has been known for long to use blood coagulating substances for stopping bleedings and for sealing wounds. According to the first proposals of this kind, fibrin tampons and fibrin platelets, respectively, were used. During the Second World War, tissue adherences by means of blood plasma were suggested.

In recent times, a tissue adhesive on the basis of fibrinogen and factor XIII for seamless interfascicular nerve transplantations in animal experiments has been described by H. Matras et al. in "Wiener Medizinischen Wochenschrift", 1972, page 517.

A further study was carried out by Spängler et al. in "Wiener Klinischen Wochenschrift", 1973, pages 1 to 7. Also there, the possibility was shown in animal experiments of carrying out a tissue adherence with the aid of fibrinogen as a cryoprecipitate and thrombin.

The known preparations have not yet proved satisfactory, since they do not sufficiently meet the demands set to a tissue adhesive, i.e.

(a) high straining capacity of the adherences and wound sealings as well as safe and permanent blood stopping, i.e. good adhering capacity of the adhesive to the wound and tissue surfaces, as well as high internal strength of the same,

(b) controllable durability of the adherences in the body,

(c) complete absorbability of the adhesive in the course of the wound healing process,

(d) wound healing stimulating properties. This may partly be due to the fact that, in the known preparations, the coagulation factors necessary for blood stopping have not been present in an optimal proportion to one another, and also to the fact that the fibrinolytic activity in the area of adherence has not been sufficiently under control. Premature dissolutions of the tissue adherences frequently occurred due to enzymatic influence.

The invention aims at avoiding these disadvantages and difficulties and has as its object to provide a lyophilized tissue adhesive of human or animal origin, which meets the demands set out further above and which is present in a lyophilized form, which is desired for its longer durability and better transporting and storing properties.

Accordingly, the invention consists in a combination of the following characteristic features:

(a) that it contains at least 33% by weight of fibrinogen,

(b) that the ratio of factor XIII to fibrinogen, expressed in units of factor XIII per gram of fibrinogen, amounts to at least 80,

(c) that in the total protein, fibrinogen and albumin are contained at a ratio of 33 to 90:5 to 40,

(d) that it has a content of plasminogen-activator-inhibitor or plasmin-inhibitor, preferably aprotinin, in an amount of 250 to 25,000 Kallikrein-inactivator-units (KIU) per gram of fibrinogen,

(e) that the preparation has been lyophilized.

According to a preferred embodiment, the tissue adhesive additionally contains glycine, whereby the resolubility of the lyophilized product is improved.

Furthermore, the tissue adhesive additionally may contain glucose or sucrose, which components also improve the solubility.

The tissue adhesive furthermore may contain 0.2 to 200 International Units (IU) of heparin per gram of fibrinogen, whereby a stabilizing effect is obtained.

The tissue adhesive according to the invention possesses characteristic cross-linking properties after the dissolution, which are determinable by the sodiumdodecyl-sulphate-(SDS)-polyacrylamide-gel-electrophoresis method. The test is carried out in that, after mixing of the tissue adhesive with an equal volume of a solution containing 40μ Moles of $CaCl_2$ and 15 NIH-units (U.S. National Institute of Health units) of thrombin per ml, the mixture is incubated at 37° C. The cross-linking degree is determined by gel electrophoresis after stopping of the reaction and reductive splitting of the disulphide bridges contained in the proteins by the addition of a mixture of urea, sodium dodecyl sulphate and β-mercaptoethanol. Typical of the tissue adhesive according to the invention is a complete cross-linking of the fibrin-γ-chains after 3 to 5 minutes, and a cross-linking of at least 35% of the fibrin-α-chains after two hours.

Fibrinogen, albumin and cold-insoluble globulin, in the total protein, are to be present in the tissue adhesive according to the invention at a certain ratio; this ratio amounts to 33 to 90:5 to 5 to 40:0.2 to 15.

The invention moreover comprises a method of producing the tissue adhesive described by starting out from a plasma cryoprecipitate, which method is characterized in that cold-soluble plasma-protein is removed from the cryoprecipitate by a single or repeated treatment with a buffer solution containing sodium citrate, sodium chloride, glycine, glucose and a plasminogen-activator-inhibitor or plasmin-inhibitor and heparin, the purified precipitate is dissolved, human albumin is added and the solution is lyophilized.

Advantageously, the cryoprecipitate has been produced of human or animal fresh plasma frozen at −20° C. When increasing the temperature to 0° to 2° C., the cryoprecipitate is gained and separated by centrifugation. The precipitate is eluted by a single or repeated elution with the buffer solution having a pH of 6 to 8.0, and centrifuged at 0° to 4° C. in order to remove the plasma-protein that is soluble in the cold. The treatment with the buffer solution is carried out until the desired factor-XIII-fibrinogen ratio is reached.

The purified precipitate is dissolved with a further buffer solution containing human albumin, glycine and, if desired, glucose or sucrose, a plasminogen-activator-inhibitor or plasmin inhibitor as well as heparin, and having a pH of 6.5 to 9.0, and is diluted to a protein concentration of 4.0 to 9.0%. The solution is filtered through a membrane filter having a pore size of down to 0.2 μm, filled into final containers and lyophilized.

The lyophilized tissue adhesive thus obtained can be stored at room temperature or preferably at +4° C.; it is ready for use after reconstitution with aqua ad iniectabilia, to which, if desired, a plasminogen-activator-inhibitor or a plasmin inhibitor, preferably aprotinin, can be added. When dissolving the lyophilized preparation, attention has to be paid that the solution ready for use contains at least 70 mg of fibrinogen per ml.

The tissue adhesive according to the invention can be applied universally. It can be used for seamless connection of human or animal tissue or organ parts, for sealing wounds and stopping bleedings as well as for stimulating wound healings.

Preferred fields of application in which the tissue adhesive can be successfully used are: indications in the field of ear, nose and throat surgery, oral surgery, dentistry, neurosurgery, plastic surgery, general surgery, abdominal surgery, thorax and vascular surgery, orthopaedics, accident surgery, urology, ophthalmology and gynaecology.

Advantageously, a mixture of thrombin and calcium chloride is added to the adhesive prior to the application of the tissue adhesive according to the invention, or is applied onto the tissues to be connected.

The method of the invention is explained in more detail by way of the following example:

21 l of human plasma, which had been frozen at −20° C., were heated to +2° C. The resulting cryoprecipitate (435 g) was separated by centrifugation at +2° C. and treated at +2° C. with 4.3 l of a buffer solution adjusted at a pH of 6.5 and containing 6.6 g of Na_3-citrate.$2H_2O$, 3.4 g of NaCl, 10.0 g of glycine, 13.0 g of glucose.$1H_2O$, 50,000 KIU of aprotinin and 200 IU of heparin per l, and again centrifuged at +2° C. The separated precipitate was dissolved in a further buffer solution having a pH of 7.9 and containing 35.0 g of human albumin, 20.0 g of glycine, 50,000 KIU of aprotinin and 200 IU of heparin per l, and diluted to a concentration of 70 mg of protein per ml.

Then the solution was sterilized by filtration through membrane filters having a pore size of down to 0.2 μm, filled into final containers at 2.2 ml each, deep-frozen and lyophilized. After reconstitution of the lyophilized product to a fibrinogen concentration of 90 mg/ml, the tissue adhesive preparation ready for use showed, in the cross-linking test, complete fibrin-γ-cross-linking after 5 minutes and 66% fibrin-α-cross-linking after 2 hours at 37° C.

The ratio of the proteins fibrinogen to albumin to cold-insoluble globulin, contained in the tissue adhesive, was determined to be 64.0:22.3:7.7. The heparin content was 4.5 IU per g of fibrinogen. Aprotinin was contained at a concentration of 1,133 KIU per g of fibrinogen. The content of factor XIII amounted to 161 units per g of fibrinogen. The total protein content in the lyophilized preparation was 72.2%, the content of fibrinogen in the lyophilized preparation was 46.2%.

The determinations were carried out in the following manner: The determination of the factor-XIII-units was performed by means of a cross-linking test, in which factor-XIII-free fibrinogen was used as a substrate and the fibrin cross-linking caused by the addition of the unknown diluted sample served as a measure for the amount of factor XIII contained therein. A corresponding calibration curve was obtained with pooled human citrate plasma, 1 ml plasma containing 1 unit of factor XIII per definitionem. The quantitative protein determinations were carried out by the method according to Kjeldahl.

The determination of the proteins relative to one another was also performed by the SDS-polyacrylamide-gel-electrophoresis method, i.e. (a) with a non-reduced sample of the tissue adhesive and (b) with a sample reduced with β-mercaptoethanol.

What we claim is:

1. A lyophilized tissue adhesive of mammalian protein origin which comprises fibrinogen, albumin, factor XIII, cold-insoluble globulin and plasminogen-activator inhibitor or plasmin inhibitor wherein the fibrinogen is present in at least 33% by weight, the ratio of factor XIII to fibrinogen, expressed in units of factor XIII per gram of fibrinogen is at least 80; and fibrinogen and albumin are present in a ratio of 33 to 90:5 to 40.

2. A tissue adhesive as described in claim 1 wherein the plasminogen-activator-inhibitor or plasmin-inhibitor is aprotinin.

3. A tissue adhesive as described in claim 1 wherein the plasminogen-activator-inhibitor or plasmin inhibitor is present in an amount which is equivalent to 250 to 25,000 KIU aprotinin per gram of fibrinogen.

4. A tissue adhesive as described in claim 1 wherein the adhesive also contains material selected from the group consisting of glycine, glucose and sucrose.

5. A tissue adhesive as described in claim 1 wherein the adhesive also contains 0.2 to 200 IU heparin per gram of fibrinogen.

6. A tissue adhesive as described in claim 1 wherein the ratio of fibrinogen to albumin to cold-insoluble globulin in the total protein is 33 to 90:5 to 40:0.2 to 15.

7. A method of producing the tissue adhesive described in claim 1 which comprises the steps of:

1. treating a cryoprecipitate with a buffer solution containing sodium citrate, sodium chloride, glycine, glucose, a plasminogen-activator-inhibitor or plasmin-inhibitor and heparin to remove cold soluble plasma protein;
2. dissolving the purified precipitate;
3. adding human albumin to the resulting solution; and
4. lyophilizing the solution.

8. A method as described in claim 7 wherein the cryoprecipitate is treated once with said buffer solution.

9. A method as described in claim 7 wherein the cryoprecipitate is treated several times with said buffer solution.

* * * * *

IMMUNO-U.S., INC.
(NEW YORK OFFICE)
950 THIRD AVENUE
NEW YORK, N.Y. 10022

Elaine ESBER, M.D.
Acting Director
Office of Biologic
Research & Review
National Center for
Drugs and Biologics
8800 Rockville Pike
Bethesda, MD 20205

Attn.: Dr. Samuel ACKERMAN

New York, May 10, 1984
MK/sch

Dear Dr. Esber,

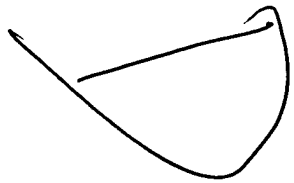
This is to submit our application for Investigational New Drug Exemption in three copies for Two-Component Fibrin Sealant, Kit, which we propose to be tested in the phase 2 studies described in the following.

Our application consists of seven volumes. Volumes one to four describe composition, manufacturing methodologies and quality control of the single substances contained in the Kit: Sealer Protein Concentrate, Fibrinolysis Inhibitor, Thrombin and $CaCl_2$. Volume five describes Two-Component Fibrin Sealant, Kit as a totality and summarizes previous preclinical and European clinical studies. Volume six contains information with respects to the studies we propose. Volume seven contains the referenced literature for your convenience.

Sincerely yours,
I M M U N O - U. S.

Encls.
threefold

Marianne Kunschak, S.M.
Head, IND Regulatory Affairs



c.c.: Dr. Eibl

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda MD 20205

AUG 2 1984

Our Reference: BB-IND 2027

EINGEGANGEN AM

20. Aug. 1984

SEKRETARIAT DIR. 6

Ms. Marianne Kunschak
Head, IND Regulatory Affairs
Immuno-U.S., Inc.
950 Third Avenue
New York, NY 10022

Dear Ms. Kunschak:

Your "Notice of Claimed Investigational Exemption for a New Drug" submitted with your letter dated May 10, 1984 was received at the Office of Biologics Research and Review, Center for Drugs and Biologics on May 21, 1984. It has been given the title "Fibrin Sealant Kit" and assigned the code number BB-IND 2027. The designation of an IND number is for identification only and does not imply endorsement or otherwise. Future correspondence and submissions concerning this "Notice" should be furnished in triplicate and referenced to the assigned IND number.

It is noted that the sponsor will not begin clinical studies with this product prior to 30 days after the receipt of this "Notice" by the Food and Drug Administration and that he will withhold or restrict clinical studies with this product if requested to do so by the Food and Drug Administration prior to the expiration of such 30 days.

Progress reports are required at intervals not exceeding one year. As part of the annual report, we would appreciate receiving the sponsor's summary of the clinical data submitted together with a current evaluation of these data with respect to the product's clinical safety and efficacy.

The interstate distribution of this product for investigational use is subject to all the conditions in Section 312.1 of the Food and Drug Regulations and may be terminated under the conditions stated in Section 312.1(d).

The lot number together with the results of all tests performed on each lot should be submitted prior to its use in clinical trials.

For any subsequent clinical protocol to be submitted under this filing, a copy of the consent form and, where applicable, the institutional review board's approval for each investigator should be submitted. For your information, we are enclosing a copy of Sections 50.20 and 50.25 of the Food and Drug Regulations which outline the general requirements for and basic elements of informed consent.

Please address all correspondence referenced to BB-IND 2027 to:

Elaine C. Esber, M.D.
Acting Director
Office of Biologics Research and Review
Center for Drugs and Biologics
Food and Drug Administration
8800 Rockville Pike
Bethesda, MD 20205

Telephone inquiries concerning this "Notice" should be made directly to the Division of Biological Investigational New Drugs at 301/443-4864.

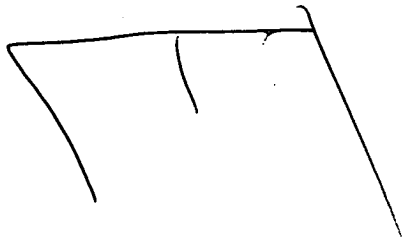
Should we have any comments following our review of this submission, we shall contact you.

Sincerely yours,

Marilyn L. Council

for Elaine C. Esber, M.D.
Acting Director
Office of Biologics Research and Review
Center for Drugs and Biologics

Enclosure



ÖSTERREICHISCHES INSTITUT FÜR HAEMODERIVATE

GESELLSCHAFT M. B. H.

PRODUKTIONSBETRIEB DER IMMUNO AKTIENGESELLSCHAFT

Elaine E. Esber, M.D.
Director
Office of Biologics
Research and Review
National Center for
Drugs and Biologics
8800 Rockville Pike
Bethesda, MD 20205
USA

INDUSTRIESTRASSE 72
A-1220 WIEN

TELEFON: (0222) 2300-0
TELEGRAMME: IMMUNO WIEN
TELEX: 134865 imuno a
134925 imuno a

Vienna, October 5, 1987
3171/Hi/MB

Re: PRODUCT LICENSE APPLICATION FOR TWO-COMPONENT FIBRIN SEALANT, KIT, TISSEEL® KIT

Dear Dr. Esber,

This is to submit our application for product licensure, i.e. Form No. 41 with Appendixes A through L in ten volumes, for TWO-COMPONENT FIBRIN SEALANT, KIT. We would appreciate your approving this application under Establishment License No. 258.

All volumes are submitted in 3 copies. Appendix K, Clinical Studies, contains, among others, the combined evaluation of two studies carried out in the U.S.A. under BB-IND No. 2027.

Please note that the present composition of THROMBIN, which is one of the 4 substances contained in TWO-COMPONENT FIBRIN SEALANT, KIT, TISSEEL® KIT, is slightly different to the composition of the IND preparation. Its albumin content has been raised from 8 mg/ml to 18 mg/ml to increase the stability of the product.

For any additional information you may require when reviewing this submission, you are kindly invited to contact

Eugene Timm, Ph.D.
Responsible Head
Immuno U.S., Inc.
1200 Parkdale Road,
Rochester, Mi 48063
Tel. (313) 652-7872

either by telephone or by mail, rather than our office here in Vienna. Dr. Timm will immediately get in touch with Dr. Eibl, Responsible Head of this Establishment, to expedite resolution of any open issues arising in connection with our submission.

Your cooperation in this matter is much appreciated.

Sincerely yours,

ÖSTERREICHISCHES INSTITUT
FÜR HAEMODERIVATE GES.M.B.H.

Hans Eibl, Ph.D.
Responsible Head

Encl.

ANDREWS OFFICE PRODUCTS CAPITOL HEIGHTS, MD (K)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Bethesda MD 20892

November 4, 1987

Hans. Eibl, Ph.D.
Oesterreichisches Institut
Fuer Haemoderivate GMBH
Industriestrasse 72
Vienna 22 AUSTRIA

Dear Dr. Eibl:

REFERENCE NUMBER 87-0509 has been assigned to your recent product license application submission for Fibrin Sealant Kit.

All future correspondence, supportive data, or labeling relating to this application should bear the above REFERENCE NUMBER and be addressed to the Director, Office of Biologics Research and Review, HHS/PHS, Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20892.

This acknowledgement does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you have the need to discuss any technical aspects of the application, you may obtain the name of the chairperson of the licensing review committee by contacting this office, 301-443-5433. Any questions concerning administrative or procedural matters should also be directed to this office.

Sincerely yours,

Sharon D. Lisso

for Donald E. Hill, Director
Division of Product Certification
Office of Biologics Research and Review

File History:

TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT

USA

Packages: 0.5mL, 1.0mL, 2.0mL, 5.0mL

Date of 1st registration: May 1, 1998

5/10/84 Sent to Elaine Esber, M.D., OBRR	Submission of IND
8/02/84 Received fromElaine Esber, M.D., OBRR	Acknowledgement of Receipt of "Notice of Claimed Investigational Exemption for a New Drug"
10/05/87 Sent to Elaine Esber, M.D., Director, OBRR	Submission of Product License Application including ELA data in Appendix G ("Description of manufacturing steps not covered by our current Establishment License No. 258")
11/04/88 Received from Donald Hill, Director, Division of Product Certification, OBRR	Acknowledgement of Receipt of PLA Submission; Assignment of Ref. No. 87-0509 and 87-0508 for PLA and ELA submissions resp.
08/26/88	Meeting at OBRR Present: FDA: Dr. Solomon, S. Preston, Dr. Fratantoni, D. Tankersley, R. Jain, M. Ying; IMMUNO: Dr. Eibl, Dr. Timm, M. Kunschak; Dr. Levitsky The following issues were raised: 1. "Provide additional information on the risk of non-A/non-B hepatitis transmission" 2. "Provide a tabulation of the safety data from the study done at the Cleveland Clinic in the format previously used for the Iveegam PLA" 3. "When did we start heating TISSEEL?"
11/10/88 Sent to Paul Parkman, M.D., Director, OBRR	PLA Supplement in reply to the issues raised in the August 26, 1988 meeting Also supplied were additional data relating to Questions 2, 4, 5, and 6 received from Sue Preston on August 11, 1988 (on an informal basis).

	These questions were: 2. "Describe the conventional therapies. If there is more than one "conventional" therapy employed, give estimates of the times used." 4. "What was the rationale for choosing the speed to determine tensile strength? Provide graphs of data to support optimum strengths." 5. "Can the 52 patients excluded because forms were not received be analyzed now? If not, does their exclusion from the analysis bias the results?" 6. "... Some patients in each group had multiple bleeding episodes. .... It would appear that each patient (treated in the U.S. study) should contribute only one success or failure."
03/02/89 Sent to Paul Parkman, M.D., Director, OBRR	PLA Supplement in follow-up of a telephone conversation with Dr. Finlayson to include data showing efficacy of each individual active ingredient
05/02/89 Sent to OBRR	Overall Application Summary
10/30/89 Received from Paul. Parkman, M.D., Director, OBRR	FDA Letter First response received with respect to the filing of the PLA in October 1987 listing the following 5 questions: 1. "With regard to the randomized study, concerns about the effectiveness of randomization remain. Data verifying the quality of randomization should be submitted. This would include establishing similarity of bleeding sites, operative time, level of medical care, etc. between groups A and B." 2. "Data on bleeding following crossover either to Fibrin Sealant or to the other agent used should be submitted. This would include duration of bleeding following crossover and information on estimated blood loss from the treated sites." 3. "Use of historical controls, whether matched or non-matched, is suspect. The matched controls should be carefully reviewed and compared to the prospective patients to be certain that the standard of care was the same in both groups. Validation that the groups are appropriately matched should be submitted." 4. "Comparison of non-matched controls from ten centers with all of the Fibrin Sealant patients disclosed a reduction in need for resternotomy, whereas a comparison of non-matched controls from center 11 with Fibrin Sealant patients from the same center showed no difference. Please comment." 5. "All deviations from protocol should be documented and explained."
04/02/90 Sent to Paul Parkman, M.D., Director, CBER	ÖIH Letter in reply to the 5 questions raised in FDA's October 30, 1989 letter (The next letter from FDA was received on May 12, 1992. It discussed the efficacy of Fibrin Sealant with respect to the efficacy of the individual active ingredients pertaining to data submitted on Marach 2, 1989.)

File History:
TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT

04/04/91 Sent to Gerald Quinnan, M.D., Acting Director, CBER	PLA Amendment including summary of the whole file for ease of reading including review of clinical data submitted and discussion of a rationale for the design of studies and endpoints used Volume I - Data already submitted; Volume II - New data including amendment to vapor heating with validation studies to support the change from dry heating to vapor heating.
10/23/91 Received from Gerald Quinnan, M.D., Acting Director, CBER	FDA Letter Requesting that product license applications should be amended to indicate that the starting plasma has been tested for anti-HCV by a licensed test and found non-reactive
01/07/92 Sent to Gerald Quinnan, M.D., Acting Director, CBER	PLA Amendment to introduce anti-HCV testing of source material
01/08/92 Received from Gerald Quinnan, M.D., Acting Director, CBER	FDA Letter to all U.S. licensed manufacturers of plasma derivatives referring to the acceptability of new procedures for inactivation of infectious agents in plasma derivatives, i.e. Factor VIII. Dr. Quinnan stated that FDA does not anticipate a need for repeated toxicity and clinical studies if a new inactivation process is adopted for existing licensed plasma products.
05/12/92 Received from Kathryn Zoon, Ph.D., Director, CBER	FDA Letter stating that a comparison of the efficacy of Fibrin Sealant with respect to topical thrombin alone could not be made based upon the data submitted in the PLA. Besides, FDA suggested animal studies to demonstrate the contribution of each ingredient of the Fibrin Sealant and asked us to submit the protocol prior to initiation of the studies. On December 28, 1992 the protocol was submitted to FDA for comment relative to testing the individual ingredients in 3 animal models under BB-IND 2027, Serial No. 054. IMMUNO did not receive any reply from FDA on this preclinical protocol. Therefore, IMMUNO assumed that the animal models were acceptable and proceeded with animal testing as described.
06/22/92	Meeting at CBER Present: FDA: Dr. Dachman, Dr. Finlayson, Dr. Gupta, Dr. Quinnan, Dr. Scribner; IMMUNO: Dr. Eibl, M. Kunschak; Dr. Herndon; Dr. Levitsky The topics were as follows: 1. Discussion of a protocol for the study of efficacy of Fibrin Sealant in burns 2. Discussion of a protocol for the preclinical study investigating the efficacy of the different components of Fibrin Sealant for their hemostatic properties

File History:
TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT

	3. Discussion of a treatment protocol
07/29/92 Sent to Kathryn Zoon, Ph.D., Director, CBER	PLA Amendment containing • minutes of the June 22, 1992 meeting • information submitted on April 2, 1990 (which had not been responded to) plus additional data specifically addressing each and every protocol dropout
09/28/93 Sent to Mary Lamb, Head, Division of Blood Establishment and Product License Applications, CBER	ÖIH Letter Referring to devices for reconstitution and application of Fibrin Sealant and including • copy of 510(k) submission filed for Duploject on September 29, 1987 and included in PLA submission of October 5, 1987 • copy of assignment of Document Control No. K874068 on October 8, 1987 • copy of letter from CDRH dated December 29, 1987 suggesting that CDRH wanted to evaluate the efficacy data submitted with the PLA before approving the device • copy of letter from Immuno to CDRH requesting withdrawal of the 510(k) submission as a consequence of the above CDRH letter • copy of letter from CDRH dated March 1, 1988 confirming closure of file
12/16/93 Received from Jay Epstein, M.D., Acting Director, CBER	FDA Letter to Immuno Clinical Research Corp., Ref. BB-IND 2027, including the following questions: 1. "Have the clinical study of Fibrin Sealant in cardiac operations and the animal studies described in the August 26, 1993 Supplement to BB-IND 2027 adequately demonstrated that a thrombin alone arm is not needed in future studies?" 2. "Have the animal experiments described in the above Supplement to BB-IND 2027 adequately demonstrated the contribution of Factor XIII to the overall clinical effect of the product? If not, can the adding back of Factor XIII to the product be viewed as "restoring" the Factor XIII level of the sealant solution to its previous inactivation step level?" 3. "If the animal experiments described in the above Supplement to BB-IND 2027 are not adequate to demonstrate the contribution of aprotinin to the overall clinical effect of the product, is there an animal model that could be used to demonstrate such a contribution? If not, is it necessary to perform a clinical trial to demonstrate the contribution of aprotinin?"
02/15/94 Sent to Kathryn Zoon, Ph.D., Director, CBER & Jay Epstein, M.D., Acting Director, CBER	ÖIH Letter proposing the following approach in response to issues raised in the December 16, 1993 letter: • Factor XIII: will not be added back after vapor heating • Aprotinin: Immuno will seek new animal models and suggests clinical trials with two different fibrin sealant preparations: a) without aprotinin for surgery in the absence of demonstrable fibrinolysis, b) with aprotinin for situations where fibrinolysis aggravates bleeding during surgery • Other studies: treatment IND should be pursued based on the prior pivotal study
03/09/94	Intent-to-Treat-Analysis

File History:
TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT

Sent to Kathryn Zoon, Ph.D., Director, CBER	of the pivotal study of Fibrin Sealant in reoperative cardiovascular surgery The data showed an unchanged significant difference of $p < 0.001$ between Fibrin Sealant and controls for the primary endpoint irrespective of whether episodes or patients were analysed.
03/22/94 Received from Jerome Donlon, M.D., Ph.D., Director, Office of Establishment Licensing and Product Surveillance, CBER	FDA Non-Approvable Letter regarding ELA The main deficiencies noted can be summarized as follows: • Narratives and diagrams of flows of product and personnel, raw materials, and waste • Validation protocols and data summaries of new or unlicensed major equipment, processes, systems • Maintenance, cleaning, and monitoring of all major equipment • Product changeover and cleaning SOPs used in the manufacturing areas • Prevention of cross-contamination • Diagrams, maintenance and routine monitoring schedules for HVAC and water systems • Environmental monitoring program for manufacturing areas • Environmental assessment
03/30/94 Sent to Jerome Donlon, M.D., Ph.D., Director, Office of Establishment Licensing and Product Surveillance, CBER	ÖIH Letter in reply to non-approvable letter stating ÖIH's intent to file an amendment to the ELA
04/13/94	Meeting at CBER The following main issues were discussed: • Final configuration of the product • Proof of efficacy of each component of the product • Need of aprotinin, Factor XIII • Human vs. bovine thrombin • Dry heating vs. vapor heating • Endpoints in cardiovascular study
07/28/94 Received from Jay Epstein, M.D., Acting Director, Office of Blood Research and Review, CBER	FDA Non-Approvable Letter regarding PLA The main deficiencies noted can be summarized as follows: • Clinical trial design and measurements of efficacy • Final product formulation • Viral inactivation Animal studies showing clinically relevant contribution of aprotinin and Factor XIII to hemostatic efficacy
08/04/94 Sent to K.C. Zoon,	ÖIH Letter (by Bruce Mackler, Ph.D., Fenwick & West) in reply to non-approvable letter stating ÖIH's intent to file an amendment to the

File History:
TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT

Ph.D., Dir., CBER & J. Epstein, M.D., Acting Director, Office of Blood Res. + Rev., CBER	PLA
8/25/95 Sent to Jay Epstein, M.D., Acting Director, Office of Blood Research and Review, CBER	ÖIH Letter in follow-up of ÖIH's letters dated March 30, 1994 and August 4, 1994 summarizing the data to be submitted for the PLA & ELA Supplements
03/06/96 Sent to Mary Padget, Office of Blood Research and Review, Division of Blood Applications, CBER	Agenda & Executive Summary for Pre-Licensing Meeting on March 28, 1996
03/28/96	Pre-Licensing Meeting at CBER
08/30/96 Sent to Jerome Donlon, M.D., Ph.D., Director, Office of Establishment Licensing and Product Surveillance, CBER	ELA Supplement referring to the Industriestrasse 131 & 72 locations and taking into account non-approvable letter of March 22, 1994
08/30/96 Sent to Jerome Donlon, M.D., Ph.D., Director, Office of Establishment Licensing and Product Surveillance, CBER	ELA Supplement referring to the Benatzkygasse location to include the manufacture of TISSEEL VH KIT at this location pending CBER approval
08/30/96 Sent to Jay Epstein, M.D.,	PLA Supplement taking into account non-approvable letter of July 28, 1994

File History:
TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT

Director, Office of Blood Research and Review, CBER	
10/15/96 Sent to Jay Epstein, M.D., Director, Office of Blood Research and Review, CBER & to Toby Silverman, M.D., Medical Officer, CBER	ÖIH Letter providing additional information (clinical) on the above PLA Supplement as requested by CBER
10/29/96 Sent to Toby Silverman, M.D., Medical Officer, CBER	ÖIH Letter providing additional information (clinical) on the above PLA Supplement as requested by CBER
01/30/97	Change of Responsible Head
02/04/97 Sent to Toby Silverman, M.D., Medical Officer, CBER	ÖIH Letter providing additional information (clinical) on the above PLA Supplement as requested by CBER
03/04/97 Received from Jay S. Epstein, M.D., Director, Office of Blood Research and Review, CBER	FDA Non-Approvable Letter regarding PLA
03/21/97	Request for a Pre-Licensing Meeting Regarding IQ-PCR Testing
04/17/97 Sent to Jerome Donlon, M.D., Ph.D., Director, Office of Establishment Licensing and Product Surveillance, CBER	Notification in reply to non-approvable ELA letter of April, 11 1997

File History:
TWO-COMPONENT FIBRIN SEALANT, VAPOR HEATED, KIT, TISSEEL® VH KIT

05/12/97	Documents Concerning the Pre-Licensing Meeting Regarding IQ-PCR Testing on May 21, 1997
05/15/97	Approval of Change of Responsible Head
08/28/97 Sent to Jerome Donlon, M.D., Ph.D., Director, Office of Establishment Licensing and Product Surveillance, CBER	ELA Supplement in reply to non-approvable letter dated April 11, 1997
11/14/97 Sent to Dr. J. S. Eppstein Director Office of Blood Research and Review FDA	Product License Application Amendment (Annotated Package Insert)
11/10-14/97	Pre-Licensing Inspection
12/16/97	BPAC meeting
01/15/98	Telefonconference (Package Insert) between: Dr. Silverman, Dr. Lynch, Ms. Padgett, Mr. Purvis, Dr. Anderle, Prof. Hans-Peter Schwarz, Dr. Igel, Dr. Hantak, Ms. Kunschak, Ms. Henninger, Dr. Vallancourt and Dr. Waites
01/21//98	Submission of revised Package Insert
05/01/98	Registration of the Product

ATTACHMENT TO PAPER NO. 12

STATEMENT OF REASONS FOR ALLOWANCE

SERIAL NO. 118,529

No art of record discloses a tissue adhiesive of the composition recited in the claims of the instant application. However, application S.N. 118,656, filed by the same inventive entity and on the same date as the instant application (2-4-80) has matured into Pat. No. 4,298,598 Pat. No. 4,298,598 discloses and claims a tissue adhesive which may contain the same ingredients as recited in the claims of the instant application Pat. No. 4,298,598 does not, however disclose or recite any thing concerning lyophilization or freeze drying, and as the claims of the instant application are limited to lyophilized tissue adhesives or a lyophilized step, it is seen that the recited proportions have a separate significance and the claims of the respective applications are patentably distinct.

A. LIEBERMAN :cac
(703) 557-3745
4-28-82

Any comments considered necessary by applicant must be submitted no later than the Issue Fee and, to avoid processing delays, should preferably accompany the Issue Fee. Such submissions should be clearly labeled *"Comments on Statement of Reasons for Allowance."*